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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,454	01/14/2002	Guido Grandi	PP01591.101	4170

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EXAMINER	
MINNIFIELD, NITA M	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/914,454	GRANDI ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,8-21,23,24,32-39 and 43-48* is/are pending in the application.

4a) Of the above claim(s) *32-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,8-21,23,24 and 43-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/20/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 20, 2010 has been entered.

2. Applicants' amendment filed September 20, 2010 is acknowledged and has been entered. Claims 5, 7, 22, 25-31 and 40-42 have been canceled. Claims 1, 23, 46 and 47 have been amended. Claims 1-4, 6, 8-21, 23, 24, 32-39 and 43-48 are now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment to the claims and/or comments, with the exception of those discussed below.

3. Claims 32-39 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 24, 2005.

4. Claims 1-4, 6, 8-21, 23, 24 and 43-48 have been examined in the instant application.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4, 6, 8-21, 23, 24 and 43-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are directed to an immunogenic composition comprising a Neisseria antigen, oligonucleotide comprising at least on CG motif (oligonucleotide is at least 6 nucleotides in length and comprises at least one phosphorothioate bond and the CG motif comprises an unmethylated CpG dinucleotide) and emulsion.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided: The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry,, whatever is now claimed. See Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, "Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104). Moreover, because the claims encompass a genus of compositions, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention

was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The Guidelines further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of compositions, the skilled artisan could not immediately recognize or distinguish members of the claimed antigenic compositions. In view of the above, the instant specification fails to meet the written description requirement as set forth under 35 U.S.C. 112, first paragraph.

A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559,1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967) ("If n-propylamine had been used in making the compound instead of n-butylamine, the compound of claim 13 would have resulted. Appellants submit to us, as they did to the board, an imaginary specific example patterned on specific example 6 by which the above butyl compound is made so that we can see what a simple change would have resulted in a specific supporting disclosure being present in the present specification. The trouble is that there is no such disclosure, easy though it is to imagine it.") (emphasis in original); Purdue Pharma L.P. v. Faulding Inc., 230 F.3d 1320, 1328, 56 USPQ2d 1481, 1487 (Fed. Cir. 2000) ("the specification does not clearly disclose to the skilled artisan that the inventors ... considered the ratio... to be part of their invention .... There is therefore no force to Purdue's argument that the written description requirement was satisfied because the disclosure revealed a broad invention from which the [later-filed] claims carved out a patentable portion").

The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. For example, even though a genetic code table would correlate a known amino acid sequence with a genus of coding nucleic acids, the same table cannot predict the native, naturally occurring nucleic acid sequence of a naturally occurring mRNA or its corresponding cDNA. Cf. In re Bell, 991 F.2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993), and In re Deuel, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995) (holding that a process could not render the product of that process obvious under 35 U.S.C. 103). The Federal Circuit has pointed out that under United States law, a description that does not render a claimed invention obvious cannot sufficiently describe the invention for the purposes of the written description requirement of 35 U.S.C. 112. Eli Lilly, 119 F.3d at 1567, 43 USPQ2d at 1405. Compare Fonar Corp. v. General Electric Co., 107 F.3d 1543, 1549, 41 USPQ2d 1801, 1805 (Fed. Cir. 1997) ("As a general rule, where software constitutes part of a best mode of carrying out an invention, description of such a best mode is satisfied by a disclosure of the functions of the software. This is because, normally, writing code for such software is within the skill of the art, not requiring undue experimentation, once its functions have been disclosed. Thus, flow charts or source code listings are not a requirement for adequately disclosing the functions of software."). MPEP 2163

A specification may describe an actual reduction to practice by showing that the inventor constructed an embodiment or performed a process that met all the limitations of the claim and determined that the invention would work for its intended purpose. Cooper v. Goldfarb, 154 F.3d 1321, 1327, 47 USPQ2d 1896, 1901 (Fed. Cir. 1998). See also UMC Elecs. Co. v. United States, 816 F.2d 647, 652, 2 USPQ2d 1465, 1468 (Fed. Cir. 1987) ("[T]here cannot be a reduction to practice of the invention without a physical embodiment which includes all limitations of the claim."); Estee Lauder Inc. v. L'Oreal, S.A., 129 F.3d 588, 593, 44 USPQ2d 1610, 1614 (Fed. Cir. 1997) ("[A] reduction to practice does not occur until the inventor has determined that the

invention will work for its intended purpose."); Mahurkar v. C.R. Bard, Inc., 79 F.3d 1572, 1578, 38 USPQ2d 1288, 1291 (Fed. Cir. 1996) (determining that the invention will work for its intended purpose may require testing depending on the character of the invention and the problem it solves). Description of an actual reduction to practice of a biological material may be shown by specifically describing a deposit made in accordance with the requirements of 37 CFR 1.801 et seq. See especially 37 CFR 1.804 and 1.809. See also paragraph I., supra. MPEP 2163 This actual reduction to practice of the claimed invention is not set forth in the instant specification.

For some biomolecules, examples of identifying characteristics include a sequence, structure, binding affinity, binding specificity, molecular weight, and length. Although structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession. >As explained by the Federal Circuit, "(1) examples are not necessary to support the adequacy of a written description; (2) the written description standard may be met … even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." Falkner v. Inglis, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). See also Capon v. Eshhar, 418 F.3d at 1358, 76 USPQ2d at 1084 ("The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes" where the genes were novel combinations of known DNA segments.).< For example, disclosure of an antigen fully characterized by its structure, formula, chemical name, physical properties, or deposit in a public depository provides an adequate written description of an antibody claimed by its binding affinity to that antigen. Noelle v. Lederman, 355 F.3d 1343, 1349, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (holding there is a lack of written descriptive support for an antibody defined by its binding affinity to an antigen that itself was not adequately described). Additionally, unique cleavage by particular enzymes, isoelectric points of fragments, detailed restriction enzyme maps, a comparison of enzymatic activities, or antibody cross-reactivity may be sufficient to show possession of the claimed invention to one of skill in the art. See Lockwood, 107 F.3d at 1572, 41 USPQ2d at

1966 ("written description" requirement may be satisfied by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention"). A definition by function alone "does not suffice" to sufficiently describe a coding sequence "because it is only an indication of what the gene does, rather than what it is." Eli Lilly, 119 F.3 at 1568, 43 USPQ2d at 1406. See also Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)).

An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.").

It is noted that Applicants have claimed a large genus of oligonucleotides comprising at least one CG motif and at least 6 nucleotides in length. The upper limit of the oligonucleotide is not defined in the claims. The specification as filed provides numerous CpG immunostimulatory nucleic acids, however the specification and claims do not indicate or give guidance in determining which of the CpG nucleic acids of the genus will function as set forth in the method of the claimed invention. Applicants "structural requirements" are so minimal as to not enable one of skill in the art to identify members of the genus. For instance, the human genome comprises approximately 2,900,000,000 nucleotides. The entire 2.9 billion nucleotides consist of only 4 nucleotides, (i.e., G, C, A, & T). Given that Applicants claims do not recite the length of the oligonucleotide (save at least 6 nucleotides in length), or the amount of space permitted between the 5' C and the G' 3, each and every DNA encoding gene in the entire genome will be encompassed by this claim. Clearly, one of skill would still not be able to identify members of

the genus, as no members appear to be excluded. Second, it appears that the oligonucleotide of the invention "can be any length greater than 6 bases or base pairs and generally comprises the CG motif comprises an unmethylated CpG dinucleotide. However, as set forth above, this still encompasses every gene in the human genome, and every gene in every other organism's genome as well. The specification asserts that the sequence 5' C-G-3' is an essential feature of of the claimed invention. However, the question remains if every gene contains the nucleotides C and G, how can this be an essential feature? One of skill in the art would simply be unable to identify the members of the genus based upon this bare bones structural requirement. This broad genus claims remain unsupported by the written description requirement. Van Uden et al (Journal of Allergy and Clinical Immunology Vol. 104, No. 5, pp 902-910, November 1999) set forth that "Even after intensive attempts to precisely define the DNA sequence structure required for immune stimulation, this most fundamental aspect of ISS is only partially understood." (See page 903). Furthermore, Fearon et al (Eur. J. Immunol. Vol. 33, pp 2114-2122, 2003) set forth that "flanking sequences" of ISS molecules can have "confounding effects." (See page 2115). Accordingly, without guidance towards a detailed structure of the oligonucleotide, which can have a profound impact on the activity of this molecule, one of skill in the art would not be able to readily identify members of the claimed genus.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406. At section B(1), the court states that "An adequate written description of a DNA... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."
A “representative number of species” means that the species, which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The

disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)(Claims directed to PTFE dental floss with a friction-enhancing coating were not supported by a disclosure of a microcrystalline wax coating where there was no evidence in the disclosure or anywhere else in the record showing applicant conveyed that any other coating was suitable for a PTFE dental floss.) On the other hand, there may be situations where one species adequately supports a genus. See, e.g., Rasmussen, 650 F.2d at 1214, 211 USPQ at 326-27 (disclosure of a single method of adheringly applying one layer to another was sufficient to support a generic claim to "adheringly applying" because one skilled in the art reading the specification would understand that it is unimportant how the layers are adhered, so long as they are adhered); In re Herschler, 591 F.2d 693, 697, 200 USPQ 711, 714 (CCPA 1979) (disclosure of corticosteroid in DMSO sufficient to support claims drawn to a method of using a mixture of a "physiologically active steroid" and DMSO because "use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description."); In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 285 (CCPA 1973) (the phrase "air or other gas which is inert to the liquid" was sufficient to support a claim to "inert fluid media" because the description of the properties and functions of the air or other gas segmentizing medium would suggest to a person skilled in the art that appellant's invention includes the use of "inert fluid" broadly.).

6. Claims 1-4, 6, 8-21, 23, 24 and 43-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunogenic composition comprising an immunostimulating amount of Neisseria antigen and an immunostimulating amount of an adjuvant (SEQ ID NO: 1 and an emulsion comprising submicron oil droplets and emulsifying agent (CFA)), does not reasonably provide enablement for immunogenic composition comprising an immunostimulating amount of Neisseria antigen and an immunostimulating amount of an adjuvant (oligonucleotide comprising at least one CG motif and an emulsion comprising submicron oil droplets and emulsifying agent). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to an immunogenic composition comprising a Neisseria antigen, oligonucleotide comprising at least on CG motif (oligonucleotide is at least 6 nucleotides in length and comprises at least one phosphorothioate bond and the CG motif comprises an unmethylated CpG dinucleotide) and emulsion. The claims do not define an upper for the length of the oligonucleotide.

The state of the art with regard to the CpG oligonucleotides and stimulating a Th-1 immune response is unpredictable. The state of the art teaches that there are a number of specific characteristics of the oligonucleotide, which are critical for its function as an immunostimulatory molecule. For instance, Krieg (BioDrugs 1998, 5:341-346) teaches that synthetic oligonucleotides ranging in length from 8 to 30 nucleotides or more could cause immune stimulation if there was only a single CpG dinucleotide as long as this was not preceded by a C or followed by a G. Most importantly, the CpG dinucleotide had to be unmethylated: if the C was replaced by s-methyl-cytosine, then the oligonucleotide lost its immune stimulatory activity (p. 342). The pending claims do not recite the upper limit of the length of the oligonucleotide. Yamamoto et al 1994 (Antisense Research and Development, 1994, 4:119-122) teaches that "immunostimulatory activity of oligonucleotides 18 bases or more in length was observed and was proportional to the base length, with a maximum at 22-30 bases. On the other hand, the oligonucleotides 16 bases or less in length were not as active even if they possessed the palindromic sequences. These results indicate that the immunostimulatory activity of oligonucleotides with certain palindromic sequences requires an oligonucleotide at least 18 bases

long." (abstract). Agrawal et al. (Trends in Mol. Med., 2002; 8:114-121) teaches that the pattern and kinetics of induction of the cytokines in vivo depends on the sequences flanking the CpG dinucleotide, as well as the dose, the route of administration and the host animal species (see page 16 "therapeutic potential of CpG DNA" in particular) and that there is a species-dependent selectivity of CpG DNA, and that the optimal CpG DNA sequences for many vertebrate species are not yet known (p. 119). Further, Agrawal et al. teach that "The presence of unmethylated CpG dinucleotide is essential for the induction of immunostimulatory activity..." (See p. 114, bottom of second column). Agrawal also teaches that sequences required for CpG related immune stimulation varies from species to species, and indicates, "The optimal motif for recognition by human immune cells is 'GTCGTT or TTCGTT" (p. 115). Thus indicating that an oligonucleotide of 6 nucleotides in length can function as an immunostimulatory agent in humans. Hartmann et al. (J. Immunology, 2000; 164:1617-1624) teaches that the oligonucleotide must be protected from nuclease degradation in order to be effective in vivo. Specifically, Hartmann teaches, "To have in vivo clinical utility, ODN must be administered in a form that protects them against nuclease degradation. The native phosphodiester internucleotide linkage can be modified to become highly nuclease resistant via replacement of one of the non-bridging oxygen atoms with a sulfur, which constitutes phosphorothioate ODN." (see p. 1618). Therefore, in order for an oligonucleotide to stimulate an immune response in vivo it must contain an unmethylated CpG motif, be at least 6 nucleotides in length, and be protected from nuclease degradation by comprising, for example, modified backbone linkage, such as a phosphorothioate linkage.

The specification as filed provides numerous CpG immunostimulatory nucleic acids, however the specification and claims do not indicate or give guidance in determining which of the CpG nucleic acids of the genus will function as set forth in the method of the claimed invention. Applicants "structural requirements" are so minimal as to not enable one of skill in the art to identify members of the genus. For instance, the human genome comprises approximately 2,900,000,000 nucleotides. The entire 2.9 billion nucleotides consist of only 4 nucleotides, (i.e., G, C, A, & T). Given that Applicants claims do not recite the length of the ISS sequence, or the amount of space permitted between the 5' C and the G' 3, each and every DNA encoding gene in the entire genome will be encompassed by this claim. Clearly, one of skill

would still not be able to identify members of the genus, as no members appear to be excluded. Second, it appears that the ISS of the invention "can be any length greater than 6 bases or base pairs and generally comprises the CG motif comprises an unmethylated CpG dinucleotide. However, as set forth above, this still encompasses every gene in the human genome, and every gene in every other organism's genome as well. The specification asserts that the sequence 5' C-G-3' is an essential feature of the claimed invention. However, the question remains if every gene contains the nucleotides C and G, how can this be an essential feature? One of skill in the art would simply be unable to identify the members of the genus based upon this bare bones structural requirement.

With regard to an immunostimulating amount of adjuvants, combination of adjuvants, it is noted that the state of the art is unpredictable. Cox et al (Vaccine, 1997, 15/3:248-256) teaches "…detail the ways in which an adjuvant can act and to attempt a classification of adjuvants based on their mode of action. The end benefit can be threefold. Firstly, if the pathogenesis of a disease is known, than an adjuvant which can generate a protective immune response can be selected for vaccine formulation. Alternatively, if the pathogenesis and immunology are not well understood, then adjuvants which can generate a range of different immune responses can be rationally selected for study. Thirdly, this knowledge can be used to combine different effects as desired." (p. 248) The purpose of adjuvant combinations is to combine various adjuvant components to achieve the desired mix of immunological responses. The best known combination is Freund's complete adjuvant (FCA) which combines the immunomodulatory properties of Mycobacterium tuberculosis (essentially TDM and MDP) along with the short-term depot effect of w/o emulsions." (p. 253) "Selection of the 'best' adjuvant combination requires some knowledge of the chemical nature of the protective immunogen(s) and some idea of the nature of the immune response which is likely to be protective. however, even where knowledge of both these issues is minimal, rational selection of a small number of basic formulations and additives should permit selection of an effective adjuvant system. It is hoped that this review will help in this rational selection." (p. 253) Cox et al teaches that emulsions can be unstable. Further, Edelman et al (Molecular Biotechnology, 2002, 21:129-148) teaches that "Every adjuvant has a complex and often multi-factorial immunological mechanism, usually poorly understood in vivo. Many determinants of adjuvanticity exist, and each adjuvanted vaccine is

unique. Adjuvant safety is critical and can enhance, retard, or stop development of an adjuvanted vaccine. The choice of an adjuvant often depends upon expensive experimental trial and error, upon cost, and upon commercial availability. Extensive regulatory and administrative support is required to conduct clinical trials of adjuvanted vaccines. Finally, comparative adjuvant trials where one antigen is formulated with different adjuvants and administered by a common protocol to animals and humans can accelerate vaccine development." (abstract) (see also, Aucouturier et al Vaccine, 2001, 19:2666-2672 and Wuorimaa et al, I. Infectious Diseases, 2001, 184:1211-1215). Aucouturier et al teaches that there are no universal adjuvants and their action is not yet clear and relies on different mechanisms. Then, they must be adapted according to several criteria, like the target species, the antigens, the type of immune response, the route of inoculation or the duration of immunity. All the above considerations for determining the use of one adjuvant are increased when the selection of a combination of immunostimulating adjuvants as instantly claimed. It would require undue experimentation to practice the claimed invention in view of the unpredictability of the length of the immunostimulatory oligonucleotide, the unmethylated CG and the problem associated with identifying a combination adjuvant.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation.'" (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The nature of the invention, breadth of the claims, unpredictability of the state of the art and state of the prior art have all been addressed above. The process of

identifying a combination adjuvant is unpredictable. The amount of additional experimentation is deemed to be undue because in order to practice the claimed invention with a reasonable expectation of success, one of skill in the art would have to show evidence overcoming art recognized problems that the broadly claimed CpG-containing oligonucleotides would be used in stimulating a Th-1 based immune response in vivo as well as combination adjuvants. The level of the skill in the art is deemed to be high (PhD level). One skill in the art would be compelled to perform undue experimentation in order to practice the claimed invention because of the large number of variables connected with the use of such nucleic acids. For example, the instant application does not give guidance as to the type of administration, the times or frequencies of administration, or the dosages required to obtain desired effects. In view of the combination of facts-- the high degree of unpredictability recognized in the art, particularly the required characteristics of the immunostimulatory oligonucleotide in order to be an effective in vivo immunostimulatory oligonucleotide as well as combination adjuvants, the breadth of the claims as mentioned above, the limited number of working examples and guidance in the specification, the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed composition is undue.

7. No claims are allowed.

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (9:00-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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